REMARKS

Claims 1-31 were pending in the application. Claims 5-8, 12-14, 17-22, 25-27, 30, and 31 have been amended. New claims 32-49 have been added. Accordingly, upon entry of the amendments, claims 1-49 will be pending in the application.

The claims have been amended to correct improper multiple dependencies. Support for the amendment to claims 5, 12, 18, 25, and 30 and new claims 32-37, 42, 48 can be found throughout the specification, including at least at 26, lines 10-13 and lines 23-26. Support for the amendment to claims 7, 14, 20, and 27 and new claims 38-39 and 46-48 can be found in the claims as filed and throughout the specification, including at least at page 18, lines 28-30; page 19, lines 4-14; and at page 29, Table II. Support for new claims 40, 41, 42, and 44 can be found throughout the specification, including at least at page 6, lines 1-29, page 6, line 34 to page 7, line 10. No new matter has been added.

Amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and were done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

The specification has been amended to include appropriate reference to trademark names and generic terminology. Applicant submits herewith a substitute specification, including a marked up version to show changes made and a clean copy. No new matter has been added.

Priority claim

The above-mentioned application claims priority to U.S. Provisional application no. 60/421262, as acknowledged by the Examiner. The applications and patents described in the "Related Applications" section of the instant specification refer to applications and patents which are related to the instant application, and are not meant to be included in the priority claim of the instant application.

Information Disclosure Statement

Applicant acknowledges the Examiner's indication that the IDS filed on January 18, 2005 has been received and will be considered in subsequent communications.

Corrected replacement specification

Applicant submits herewith a replacement specification which includes corrections, including those requested by the Examiner regarding trademark indications and the correction of the word "TNF" at page 26, line 13.

Rejection of Claims 1-4, 7-11, 14-17, 20-24, 27-29 and 31 Under 35 U.S.C. 112, First Paragraph

The Examiner has rejected claims 1-4, 7-11, 14-17, 20-24, 27-29 and 31 under 35 U.S.C. 112, first paragraph for failing to enable the claimed invention and for failing to comply with the written description requirement with regard to the term "TNFα inhibitor.'" Applicant respectfully traverses this rejection.

The Examiner states that based on the use of the term "TNFα inhibitor," the "instant claims encompass in their breadth any agent which inhibits signaling via TNFα," which the Examiner claims is not enabled by the instant specification. In contrast to the Examiner's assertion, Applicant provides ample support to enable one of ordinary skill in the art to perform the methods of the claimed invention. The term "TNFα inhibitor" is defined in the specification at page 5, lines 11-14 as an agent which inhibits TNFα, wherein Applicant further provides a list of examples of TNFα inhibitors, including etanercept, infliximab, human anti-TNFα monoclonal antibodies, CDP 571, and CDP 870. The specification also describes the efficacy of three different TNFα inhibitors, including a chimeric antibody, a human antibody, and a fusion protein, using the low dose methods of the invention. As described at page 27, lines 20-26, a range of doses for each of the three TNFα inhibitors was administered to mice using an upper limit dose of 10 mg/kg and a lower limit dose of 0.01 mg/kg. The results demonstrate that mice treated with the various TNFα inhibitors show improvements in their symptoms, including a decrease in joint inflammation and damage, as well as weight gain. The examples provided by the Applicant demonstrate that the three exemplary TNFα inhibitors are effective in

dosage ranges well below the high, saturating doses demonstrated to be the most effective.

The Examiner is of the opinion that

> [a] person skilled in the art is not enabled to make and use any agent which modulates signaling via TNFα commensurate with the scope of the claims...because it was well known in the art at the time the invention was made that molecules having highly diverse structural and biochemical properties can modulate signaling.

The Examiner also presents a reference in support of this assertion. Applicant submits that one of ordinary skill in the art cannot identify a TNFα inhibitor to be used in the methods of the invention merely based on its structure, but rather the artisan would determine a potential TNFα inhibitor using standard assays known in the art. For example, a TNFα inhibitor may be selected based on its ability to inhibit TNFα activity in a standard *in vitro* assay such as the L929 neutralization assay (see page 7, line 1 of specification). The claimed invention is directed to a low dose method for treating disorders in which TNFα activity is detrimental and is not directed to compositions comprising agents which could be used in the methods of the invention. One of ordinary skill in the art would recognize based on the teachings in the specification and the knowledge in the art at the time of filing that *any compound which inhibits TNFα may be used in a low dose therapy of the invention*. Applicant's discovery of the benefits of a low dose treatment using TNFα inhibitors is not limited to a particular type of agent, but rather to any agent which inhibits TNFα. Thus, Applicant submits that one of ordinary skill in the art could perform the methods of the claimed invention based on the teachings of the instant specification and the knowledge in the art at the time of filing.

Furthermore, the claimed methods may be used with any TNFα inhibitor, including those explicitly described in the specification. The examples provided in the specification demonstrate that a low dose method of the invention can be used regardless of the nature of the TNFα inhibitor. Applicant submits that the examples provided in the specification were not meant to limit the claimed invention. As such, Applicant should not be limited to the agents included in the working examples.

The Examiner also asserts that Applicant was not in possession of the claimed invention at the time of filing, and states that the specification does not "provide a sufficient number of representative species to support a genus of 'inhibitors.'" Contrary to the Examiner's assertion, the specification discloses numerous examples of TNFα inhibitors sufficient to describe the genus as a whole. As described above, Applicant describes a number of examples of different types of TNFα inhibitors, and, furthermore, provides working examples of three different types of TNFα inhibitors. Applicant respectfully points out that "a 'representative number' is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (see MPEP 2163(II.A.3.a.ii). As discussed above, Applicant clearly demonstrates possession of the claimed invention, as the necessary feature of the TNFα inhibitor is that it can inhibit TNFα. Applicant respectfully requests that the rejection of claims 1-4, 7-11, 14-17, 20-24, 27-29 and 31 under 35 U.S.C. 112, first paragraph, be withdrawn.

Rejection of Claims 1-6, 8-13, 15-19, 21-26, and 28-31 Under 35 U.S.C. 112, Second Paragraph

I. Rejection of claims 1-6, 8-13, 15-19, 21-26, and 28-31

The Examiner has rejected claims 1-6, 8-13, 15-19, 21-26, and 28-31 under 35 U.S.C. § 112, second paragraph for recitation of the phrase "low dose." The Examiner states that definition of the term "low dose" as described in the specification is "vague and indefinite." Applicant respectfully traverses the foregoing rejection on the grounds that claims 1-6, 8-13, 15-19, 21-26 and 28-31 particularly point out and distinctly claim the subject matter which Applicant regards as their invention, as required by 35 U.S.C. § 112, second paragraph.

Applicant submits that based on the plain language of the claims and the teachings in Applicant's specification, claims 1-6, 8-13, 15-19, 21-26 and 28-31 are clear and definite to one of ordinary skill in the art. The specification teaches at page 7, lines 11-14 that the phrase "low dose" means an amount of a TNFα inhibitor which is substantially lower than that ordinarily employed. Thus, by definition a

low dose therapy or a low dose method of the invention is meant to be a method comprising administering an amount of a TNFα inhibitor which is substantially lower than that normally prescribed. In addition to clearly defining the term "low dose," Applicant provides working examples which describe exemplary dosage amounts of a low dose treatment using an animal model for arthritis. Pages 27-30 and Figures 1-6 of the instant specification include results from animal studies which examine the efficacy of three TNFα inhibitors, *i.e.,* etanercept, infliximab, and D2E7, at relieving symptoms associated with RA in a murine rheumatoid arthritis (RA) model. Applicant teaches at page 30, lines 5-19, that low doses of each TNFα inhibitor are effective at improving disease activity within the joints, such as cartilage erosion, despite the fact that the same low doses appear less effective when the mice are examined for improvements in their arthritic score (see Figures 1-4).

In addition to the teachings of the specification, one of ordinary skill in the art could easily determine the dose of the specific TNFα inhibitor ordinarily given to a subject for treatment of a disorder in which TNFα activity is detrimental. Based on this knowledge, one of ordinary skill in the art could determine that a low dose used in the methods of the invention includes an amount lower than the normally prescribed dose. For example, it is common knowledge to one of ordinary skill in the art that the amount of D2E7 (also known as Humira®) ordinarily employed for the treatment of rheumatoid arthritis is 40 mg. Thus, low doses which are substantially lower than 40 mg would be recognized by the one of ordinary skill as being included in the low dose methods of the invention. Applicant respectfully requests that the rejection of claims 1-6, 8-13, 15-19, 21-26, and 28-31 under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

II. Rejection of claims 6, 13, 19, and 26

The Examiner has rejected claims 6, 13, 19, and 26 as containing trademark names. Applicant has amended claims 6, 13, 19, and 26 to refer to the generic name of Enbrel® and Remicade®, *i.e.,* etanercept and infliximab. In view of the amendments, the rejection is rendered moot.

Rejection of Claims 1- 31 Under 35 U.S.C. 102(b)

The Examiner has rejected claims 1-31 under 35 U.S.C. 102(b) as lacking novelty in view of U.S. Patent No. 6,258,562 (Salfeld *et al.*). Applicant respectfully traverses this rejection.

Applicant's invention is directed to a method for treating a disorder in which TNFα activity is detrimental comprising administering to a subject an effective amount of a TNFα inhibitor in a low dose therapy, such that the disorder is treated. Applicant's invention is also directed to a low dose method to alleviate symptoms associated with a disorder in which TNFα activity is detrimental, comprising administering a low dose of a TNFα inhibitor to a subject suffering from said disorder, such that the symptoms are treated. The claimed invention further describes a method of sequestering TNFα into complexes in a subject suffering from a disorder in which TNFα activity is detrimental, by administering a low dose of a TNFα inhibitor to the subject.

Applicant's invention is based on the discovery of the benefits of administering low doses of a TNFα inhibitor. In the working example, Applicant teaches that D2E7 eliminates arthritis in transgenic mice at doses ranging from 1 mg/kg to 10 mg/kg (see Figure 1), whereas lower doses, *e.g.,* 0.1 to 0.01 mg/kg, fail to eliminate the disorder. Interestingly, upon further investigation of the treated mice, Applicant discovered that lower amounts of D2E7, *e.g.,* 0.1 mg/kg, also provided therapeutic benefits which were not evident through standard arthritic assays, such as the arthritic score. Applicant identifies benefits to administering low doses of the antibody, including improving cartilage erosion, as shown in Table 2 at page 29 of the specification. Applicant also teaches in the specification that low doses of TNFα inhibitor may be advantageous as they may decrease side effects and may decrease the frequency of administration associated with the normally prescribed dose (see specification at page 7, lines 20-22).

Under 35 U.S.C. 102, for a prior art reference to anticipate a claimed invention, the prior art must teach *each and every element* of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987). Furthermore, "the identical invention must be shown in as complete detail as is contained in the...claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Applicant respectfully submits that the

Examiner has failed to establish how Patent '562 teaches each and every element of the claimed invention in accordance with 35 U.S.C. §102.

U.S Patent No. 6,258,562 (hereinafter the '562 patent) teaches compositions and methods of use relating to human anti-TNFα antibodies, including the antibody D2E7. The Examiner states that the '562 patent teaches "an effective dose of the antibody is 0.1-20 mg/kg." The Examiner also states "[s]ince the same disorder is treated by Salfeld *et al.* as disclosed in the instant application, the symptoms of the disorder are inherently the same. Therefore there is no manipulative difference between the claimed method and the method taught by the prior art."

The claimed invention specifies a method comprising administering *a low dose* of a TNFα inhibitor. Applicant respectfully submits that there is no teaching or suggestion in the '562 patent to administer a dose of a TNFα inhibitor which is less than that ordinarily used for treatment. In contrast to Applicant's invention, the '562 patent does not teach or suggest administering a low dose of TNFα inhibitor, nor does the '562 patent teach or suggest examining doses which are lower than those normally prescribed to determine if there are additional benefits. Applicant submits that the dose ranges presented in the '562 patent relate to optimal amounts suggested for prescribing the antibody for treatment, which correspond to the ordinarily employed amounts which Applicant uses to determine the low dose with which to administer in the claimed methods. Furthermore, in contrast to the Examiner's assertion, Applicant is not attempting to claim treatment of symptoms of disorders which are described in the '562 patent, but rather Applicant's invention is directed to a new low dose method of treatment for said disorders and symptoms. Applicant respectfully requests that the 102(b) rejection in view of the '562 patent be reconsidered and withdrawn, as the '562 patent does not teach each and every element of the claim.

Rejection of Claims 1- 31 Under 35 U.S.C. 102(e)

The Examiner has rejected claims 1-31 under 35 U.S.C. 102(e) as lacking novelty in view of U.S. Patent No. 6.509,015 (Salfeld *et al.*). Applicant respectfully traverses this rejection.

U.S Patent No. 6,509,015 (hereinafter the '015 patent) teaches compositions and methods of use relating to human anti-TNFα antibodies, including the antibody D2E7. Further to the comments presented above regarding the '562 patent, Applicant

submits that the '015 patent also does not anticipate the claimed invention as there is no suggestion by the '015 patent to look below the normally prescribed dosage amount for low doses for decreasing disease activity. There is no teaching in the '015 patent to consider doses which appear less efficacious in standard assays than saturating doses, as described by Applicant. In addition, Applicant maintains with regard to the '015 patent that the claimed method is not directed solely to the treatment of symptoms of disorders which are described in the '015 patent, but rather to a new low dose method of treatment for said disorders and symptoms. Thus, Applicant respectfully requests that the 102(e) rejection in view of the '015 patent be reconsidered and withdrawn, as the '015 patent does not teach each and every element of the claim as required under 102(e).

Rejection of Claims 1- 31 Under Obviousness-Type Double Patenting

The Examiner has rejected claims 1-31 the judicially created doctrine of obviousness-type double patenting as being unpatentable in view of claims 1-100 of U.S. Patent No. 6.509,015 (Salfeld *et al.*; hereinafter the '015 patent). In particular, the Examiner is of the opinion that

> [c]laims 1-100 of U.S. Patent No. 6,509,015 are directed to a method of treating a disease, such as rheumatoid arthritis, by administering an anti-TNFα antibody, alone or in combination with additional therapeutic agents. The specification clarifies at columns 2-3, bridging paragraph, that the antibody identified in the claims by SEQ ID NOS is the D2E7 antibody, i.e. the same antibody as recited in the instant claims. Since the treatment of the same disorder is claims in U.S. Patent No. 6,509,015 as in the instant application, the symptoms of the disorder are inherently the same, and therefore are not patentably distinct from the instant claimed invention.

Applicant respectfully traverses the aforementioned obviousness-type double patenting rejection on the grounds that the low dose methods of treatment of claims 1-31 would not have been obvious over the generic claims of U.S. Patent 6.509,015.

A nonstatutory basis exists for a double patenting rejection when the claimed invention is an obvious variation of an invention in an issued patent (MPEP 804(B)(1)). Accordingly, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). To establish a

prima facie case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). ***The prior art reference must teach or suggest all of the claim limitations*** (M.P.E.P. 2143).

Furthermore, Applicant respectfully submits that "[t]he fact that a claimed species or subgenus is encompassed by a ... genus is not sufficient by itself to establish a *prima facie* case of obviousness." *In re Baird*, 16 F.3d 380, 382 (M.P.E.P 2144.08). Moreover, the fact that a claim in one patent or patent application "dominates" subject matter claimed in another patent or patent application does not, by itself, give rise to double patenting. *In re Kaplan* 789 F.2d 1574 (Fed. Cir. 1986).

In the present case, the claimed invention is directed to a low dose therapy for treating a disorder in which TNFα activity is detrimental wherein a low dose of a TNFα inhibitor is administered to a subject. The claimed invention is also directed to a method of alleviating symptoms associated with a disorder in which TNFα activity is detrimental comprising administering a low dose of a TNFα inhibitor to a subject. The claimed invention is further directed to a method of sequestering TNFα into complexes in a subject suffering from a disorder in which TNFα activity is detrimental, wherein a low dose of a TNFα inhibitor is administered to a subject having said disorder.

The methods of the invention are unique in that they embody Applicant's discovery that low doses of TNFα inhibitors, below those normally used for the treatment of the claimed disorders, can be effective at treating said disorders and alleviating symptoms associated with said disorders. The claimed invention is specific to *low dose therapy* and does not include general treatment of the symptoms associated with disorders as referred to by the Examiner. The methods of the

invention include dosages not shared by a large number of the methods of the claimed genus in the '015 patent. Moreover, Applicant respectfully submits that one of ordinary skill in the art would not have been motivated to arrive at the claimed invention, *i.e.*, to select the claimed species, based on the genus disclosed in the '015 patent (see M.P.E.P 2144.08). The '015 patent does not teach or suggest using low doses of a TNFα inhibitor, but rather provides general guidance with regard to normally prescribed dosing. In summary, the claimed invention is directed to a patentably distinct species of low dose therapy and, similar to the *In re Baird* case, this species would not have been obvious over the large size of genus disclosed in the '015 patent.

In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw this obviousness-type double patenting rejection of claims 1-31.

Provisional Rejection of Claims 1- 31 Under Obviousness-Type Double Patenting

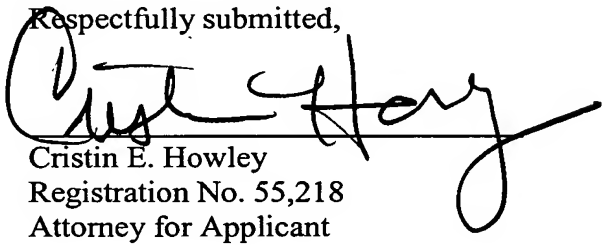
The Examiner has provisionally rejected claims 1-31 under the judicially created doctrine of obviousness-type double patenting as being unpatentable in view of claims 47-56 in Applicant's co-pending application U.S. 10/302,356. Applicant respectfully points out that claims 47-56 were cancelled in a Preliminary Amendment filed in connection with U.S. Application No. 10/302,356 and are no longer pending. In view of the cancellation of claims 47-56, Applicant submits that the provisional rejection of claims 1-31 under the judicially created doctrine of obviousness-type double patenting in view of U.S. Appln. No. 10/302,356 is rendered moot.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicant's agent would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicant's agent at (617) 227-7400.

In addition, Applicant includes herewith authorization to charge fees associated with new claims and the extension of time with which to respond, to our Deposit Account No. 12-0080, under Order No. BBI-190. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. BBI-190.

Respectfully submitted,



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